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<b>(21) International Application Number:</b> PCT/US97/22177 <b>(22) International Filing Date:</b> 5 December 1997 (05.12.97) <b>(30) Priority Data:</b> 96/15580 17 December 1996 (17.12.96) FR <b>(71) Applicant:</b> WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). <b>(72) Inventors:</b> CADE, Dominique; 11, rue des Americains, F-68000 Colmar (FR). HE, Xiongwei; 20, rue Ed. Richard, F-68000 Colmar (FR). SCOTT, Robert, Anthony; Koninin Elisabethplein 26, Bus 4, B-9100 Sint-Niklaas (BE). <b>(74) Agents:</b> RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.	<b>(81) Designated States:</b> AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
<b>(54) Title:</b> POLYMER FILM COMPOSITIONS FOR CAPSULES  <b>(57) Abstract</b>  The present invention relates to non-animal polymer compositions suitable for film forming, particularly hard and soft capsules, comprising water soluble cellulose ethers, hydrocolloides and sequestering agents.		

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## POLYMER FILM COMPOSITIONS FOR CAPSULES

### Background of the Invention

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#### 1. Field of the Invention

The present invention relates to non-animal polymer compositions suitable for film forming, particularly hard and soft capsules, comprising water soluble cellulose ethers,  
10 hydrocolloids and sequestering agents.

#### 2. Description of Related Art

Capsules are widely used in the pharmaceutical industry as well as in the health food supplement market. The main usage thereof is as dosage form for solid, semi-solid, liquid,  
15 pellet or herbal preparations. A primary objection of these dosage forms is to have a good disintegration after being administered in order to enable an effective dissolution of the active substances in the appropriate digestive organ. Consequently, this disintegration characteristic has to remain stable over time when finished products are stored prior to use.

The traditional material for forming the capsule shell is gelatin, because it has the  
20 correct and quite ideal properties. Nevertheless, gelatin has some disadvantages which make it necessary to have other capsule shell materials available. A major unfavorable aspect is the animal origin of gelatin. Other disadvantages are the inconveniences of relatively high water content (10-17%) and the loss of elasticity with decreasing water content. Furthermore gelatin capsules are sensitive to heat and humidity which affects the usability of the product. In  
25 particular, soft gelatin capsules are known to aggregate under hot and humid conditions. Under dry conditions gelatin films may induce static charge build up affecting later processing.

As a gelatin substitute the use of water soluble film forming cellulose derivatives is widely described in the literature. Reports of capsules made from cellulose derivatives refer to poor disintegration in vivo especially when compared with gelatin. To overcome this drawback in EP0714656 it is suggested to use hydroxypropylmethylcellulose (HPMC) with a viscosity of 2.4 to 5.4 centistokes in 2% aqueous solution at 20°C with carrageenan as gelling agent and calcium or potassium ions as co-gelling agent. However the very low viscosity of HPMC resulting from lower molecular weight chains induces higher film brittleness. Furthermore, the use of this composition results in an undesirable loss of transparency of the film. Attempts to improve transparency are disclosed in EP0592130 by exposing HPMC to UV radiation prior to capsule processing.

#### **Summary of the Invention**

It has been found that a polymer film composition for capsules wherein the ratios of cellulose ethers, hydrocolloids and sequestering agents are 90 to 99.98% by weight of a cellulose ether or mixture of cellulose ethers with a water content of 2 to 10%, 0.01 to 5% by weight of a hydrocolloid or mixtures of hydrocolloids, and 0.01 to 5% by weight of a sequestering agent or agents do not have the mentioned disadvantages.

#### **Detailed Description of the Preferred Embodiments**

Suitable cellulose ethers for the present invention are alkyl- and/or hydroxyalkyl substituted cellulose ether with 1 to 4 carbon atoms in the alkyl chains, preferably methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxyethylethyl cellulose, hydroxypropylmethyl cellulose or the like. Especially preferred is HPMC. The amount of the cellulose ether or mixture of cellulose ethers is preferably 95 to

99.98% by weight. The viscosity of the cellulose ether or blend is 3 to 15 cps in 2% aqueous solution at 20°C, preferred 5 to 10, especially preferred 6 cps.

Suitable hydrocolloids include such items as synthetic gums which are capable of gelling without the addition of alkaline or alkaline earth metal ions. The preferred gum for this purpose is gellan gum. Such gum, particularly including gellan gum, may be combined in mixtures producing synergistic properties which mixtures may also include natural seaweeds, natural seed gums, natural plant exudates, natural fruit extracts, bio-synthetic gums, bio-synthetic processed starch or cellulosic materials. More specifically, the mixture may include alginates, agar gum, guar gum, locust bean gum (carob), carrageenan, tara gum, gum arabic, ghatti gum, Khaya grandifolia gum, tragacanth gum, karaya gum, pectin, arabian (araban), xanthan, gellan, starch, Konjac mannan, galactomannan, funoran, and other exocellular polysaccharides of which are preferred the exocellular polysaccharides, such as xanthan, acetan, gellan, welan, rhamsan, furcelleran, succinoglycan, scleroglycan, schizophyllan, tamarind gum, curdlan, pullulan, dextran. The amount of gum present is preferably 0.01 to 2% by weight and especially preferred 0.1 to 1.0%.

The preferred sequestering agents are ethylenediaminetetraacetic acid, acetic acid, boric acid, citric acid, gluconic acid, lactic acid, phosphoric acid, tartaric acid or salts thereof, methaphosphates, dihydroxyethylglycine, lecithin or beta cyclodextrin and combinations thereof. Especially preferred is ethylenediaminetetraacetic acid or salts thereof or citric acid or salts thereof. The amount is preferably 0.01 to 3%, especially 0.1 to 2% by weight.

The sequestering mechanism can be adjusted by addition of either monovalent or divalent cations, such as  $\text{Ca}^{++}$ ,  $\text{Mg}^{++}$ ,  $\text{K}^+$ ,  $\text{Na}^+$ ,  $\text{Li}^+$ ,  $\text{NH}_4^+$  or the like.

Capsules or films with the inventive polymer composition may be manufactured with conventional machines by the conventional processes like extrusion moulding, injection moulding, casting or dip moulding.

The capsules and films have a non-animal polymer composition, an improved dissolution behavior, an enhanced elasticity and show higher transparency. The enhanced elasticity makes the capsules more useful for inhalation products. Furthermore the capsules are not sensitive to formaldehyde, for e.g. from a contaminated fill and they have a better

5 temperature stability compared to gelatin capsules, because a crosslinking at storage on elevated temperatures does not occur.

The inventive polymer composition may contain additionally acceptable plasticizers in a range from about 0 to 40% based upon the weight of the cellulose ether. Suitable plasticizers are polyethylene glycol, glycerol, sorbitol, sucrose, corn syrup, fructose, dioctyl-sodium

10 sulfosuccinate, triethyl citrate, tributyl citrate, 1,2-propyleneglycol, mono-, di- or triacetates of glycerol, natural gums or the like as well as mixtures thereof.

The inventive polymer composition may contain in a further aspect additionally pharmaceutically or food acceptable coloring agents in the range of from about 0 to about 10% based upon the weight of the cellulose ether. The coloring agents may be selected from azo-,

15 quinophthalone-, triphenylmethane-, xanthene- or indigoid dyes, iron oxides or hydroxides, titanium dioxide or natural dyes or mixtures thereof. Examples are patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D+C red 33, D+C red 22, D+C red 26, D+C red 28, D+C yellow 10-, yellow 2G, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, brilliant black BN, carbon black,

20 iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, anthocyanines, turmeric, cochineal extract, chlorophyllin, canthaxanthin, caramel, or betanin.

Color

The shaped polymer composition of the invention or the final product thereof may be coated with a suitable coating agent like cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylic acid polymers, hypromellose phthalate, hydroxypropylmethyl cellulose

phthalate, hydroxyalkyl methyl cellulose phthalates or mixtures thereof to provide e.g. enteric properties.

5 The polymer composition of the invention may be used for the production of containers for providing unit dosage forms for example for agrochemicals, seeds, herbs, foodstuffs, dyestuffs, pharmaceuticals, flavoring agents and the like.

capsule filling

The improved elasticity of the inventive polymer composition makes it useful for the encapsulation of caplets in a capsule, especially in a tamper-proof form. The encapsulation of a caplet in a capsule is preferred processed by cold shrinking together capsule parts, which are filled with a caplet, which comprises the steps providing empty capsule parts, filling at least  
10 one of said capsule parts with one or more caplets, putting said capsule parts together, and treating the combined capsule parts by cold shrinking.

The inventive polymer composition is also useful for encapsulating and sealing the two capsule halves in a process in which one or more layers of the composition are applied over the seam of the cap and body, or by a liquid fusion process wherein the filled capsules are wetted  
15 with a hydroalcoholic solution that penetrates into the space where the cap overlaps the body, and then dried.

The improved properties of the polymer composition are demonstrated by the following composition and comparative examples.

**COMPOSITION EXAMPLES:**

<u>COMPONENTS</u>	<u>COMPOS 1</u>	<u>COMPOS. 2</u>	<u>COMPOS. 3</u>	<u>COMPOS. 4*</u>
HPMC (1)	99.26%	99.62%	99.46%	98.1%
Gellan	0.54%	0.22%	0.54%	0
Na citrate	0.20%	0	0	0
Citric Acid	0	0.16%	0	0
Carrageenan	0	0	0	1.3%
KCl	0	0	0	0.6%

\* According to EP0714656

(1) HPMC equilibrated at 50% RH (equivalent to a water content between 5 to 7%)

5 Composition 5: Conventional transparent hard gelatin capsule

Composition 6: Conventional opaque hard gelatin capsule

**Mechanical impact test:**

Capsule body parts are submitted to mechanical impact stress of 80 mJ and the percentage of

10 fractured capsules are checked.

<u>EQUILIBRIUM</u>	<u>COMPOS. 1</u>	<u>COMPOS. 2</u>	<u>COMPOS. 5</u>	<u>COMPOS. 6</u>
<u>RH</u>				
50%	0	0	0	0
10%	0	0	0	5
2.5%	0	0	10	45



**Inhalator piercing test:**

Capsules are pierced by inhalator device and the percentage of cracks and/or fracture is recorded.

<u>EQUILIBRIUM</u>	<u>COMPOS. 1</u>	<u>COMPOS. 2</u>	<u>COMPOS. 5</u>	<u>COMPOS. 6</u>
<u>RH</u>				
50%	0	0	0	0
10%	0	0	95	80
2.5%	0	0	95	75

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**Capsule transparency test:**

Capsule bodies are measured for transmittance at 650 nm

<u>CAPSULE</u>	<u>TRANSPARENCY</u>
Composition 1	74%
Composition 2	75%
Composition 4	60%
Composition 5	81%

**Dissolution test:**

- 10 Acetaminophen dissolved from capsules immersed in deionised water at 37°C (USP XXIII), listed is the percentage of acetaminophen after 45 min.

<u>CAPSULE</u>	<u>% DISSOLVED</u>
Composition 1	90%
Composition 2	90%
Composition 3	63%
Composition 5	91%

**Dissolution test after exposure to crosslinking agent:**

- Capsules were filled with lactose containing 40 ppm of HCHO and stored under room conditions for one month, measured is the percentage of acetaminophen dissolved after 45 min.

<u>CAPSULE</u>	<u>% DISSOLVED</u>
Composition 1	90%
Composition 5	22%

**Moisture exchange test:**

- Capsules were filled with dry carboxymethylcellulose sodium salt (CMC) and stored in closed bottle under room conditions.

<u>CAPSULE</u>	<u>INITIAL WATER CONTENT</u>		<u>FINAL WATER CONTENT</u>	
	<u>Capsule</u>	<u>Fill</u>	<u>Capsule</u>	<u>Fill</u>
Composition 1	6.4%	0%	1.4%	1.1%
Composition 5	14%	0%	4.7%	2.0%

**CLAIMS:**

1. Non-animal polymer compositions for film forming comprising a cellulose ether  
or mixtures of cellulose ethers, a hydrocolloid or mixtures of hydrocolloids, wherein said  
5 hydrocolloids or mixtures of hydrocolloids comprise gellan gum, either singularly or in  
mixtures with other polysaccharides and a sequestering agent or mixtures thereof.
2. A polymer composition according to claim 1 wherein the ratio of cellulose  
ether, hydrocolloid and sequestering agent is
  - 10 a) 90 to 99.98% by weight of a cellulose ether or mixture of cellulose ethers with  
a water content of 2 to 10%;
  - b) 0.01 to 5% by weight of a hydrocolloid or mixtures of hydrocolloids, and
  - c) 0.01 to 8% by weight of a sequestering agent or mixtures of sequestering  
agents.
- 15 3. A polymer composition according to claims 1 or 2, wherein the cellulose ether  
or mixture of cellulose ethers is selected from alkyl- and/or hydroxyalkyl substituted  
cellulose ethers with 1 to 4 carbon atoms in the alkyl chains.
- 20 4. A polymer composition according to claim 3, wherein the cellulose ether or  
mixture of cellulose ethers is selected from methyl cellulose, hydroxyethyl cellulose,  
hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxyethylethyl cellulose,  
hydroxypropylmethyl cellulose.

5. A polymer composition according to claim 4, wherein the cellulose ether is hydroxypropylmethyl cellulose.
6. A polymer composition according to claims 1 or 2, wherein the hydrocolloid or mixture of hydrocolloids is selected from polysaccharides.
7. A polymer composition according to claim 6, wherein the hydrocolloid or mixture of hydrocolloids also includes one or more of alginates, agar gum, guar gum, locust bean gum (carob), carrageenan, tara gum, gum arabic, ghatti gum, Khaya grandifolia gum, tragacanth gum, karaya gum, pectin, arabian (araban), xanthan, starch, Konjac mannan, galactomannan, funoran or exocellular polysaccharides such as acetan, welan, rhamsan, furcelleran, succinoglycan, scleroglycan, schizophyllan, tamarind gum, curdlan, pullulan or dextran.
8. A polymer composition according to claim 2, wherein the sequestering agent or mixture of sequestering agents is selected from ethylenediaminetetraacetic acid, acetic acid, boric acid, citric acid, gluconic acid, lactic acid, phosphoric acid, tartaric acid or salts thereof, metaphosphates, sodium hexametaphosphate, dihydroxyethylglycine, lecithin or beta cyclodextrin.
9. A polymer composition according to claim 8, wherein the sequestering agent or mixture of sequestering agents is selected from ethylenediaminetetraacetic acid or salts thereof or citric acid or salts thereof.
10. A polymer composition according to claim 1 wherein

- a) the cellulose ether or mixture of cellulose ethers is contained in an amount of 95 to 99.98% by weight;
- b) The polysaccharide or polysaccharide mixture is contained in an amount of 0.01 to 2% by weight, and
- 5 c) the sequestering agent is contained in an amount of 0.01 to 3% by weight.

11. A polymer composition according to claim 1 wherein the cellulose ether or mixture of cellulose ethers has a viscosity of 3 to 15 cps measured in a 2% aqueous solution at 20°C.

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12. A polymer composition according to claim 11, wherein the cellulose ether or mixture of cellulose ethers has a viscosity of 5 to 10, preferred 6 cps measured in a 2% aqueous solution at 20°C.

15 13. A polymer composition according to claim 1 containing additionally plasticizers in a range from about 0 to 40% based upon the weight of the cellulose ether.

14. A polymer composition according to claim 13 wherein the plasticizer or mixture of plasticizers is selected from polyethylene glycol, glycerol, sorbitol, sucrose, corn syrup, fructose, dioctyl-sodium sulfosuccinate, triethyl citrate, tributyl citrate, 1,2-propylenglycol, mono-, di- or triacetates of glycerol, or natural gums.

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15. A polymer composition according to claim 1 containing additional coloring agents in a range from about 0 to 10% based upon the weight of the cellulose ether.

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16. A polymer composition according to claim 15 wherein the coloring agent or mixture of coloring agents is selected from azo-, quinophthalone-, triphenylmethane-, xanthene- or indigoid dyes, iron oxides or hydroxides, titanium dioxide or natural dyes.
- 5 17. A polymer composition according to claim 15 wherein the coloring agent or mixture of coloring agents is selected from patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D+C red 33, D+C red 22, D+C red 26, D+C red 28, D+C yellow 10, yellow 2 G, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, or brilliant black BN.
- 10 18. A polymer composition according to claim 15 wherein the coloring agent or mixture of coloring agents is selected from carbon black, iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, anthocyanines, turmeric, cochineal extract, chlorophyllin, canthaxanthin, caramel, or betanin.
- 15 19. Containers for unit dosage forms for agrochemicals, seeds, herbs, foodstuffs, dyestuffs, pharmaceuticals, or flavoring agents produced from the polymer compositions according to claim 1.
- 20 20. A container according to claim 19 which is in the form of a pharmaceutical capsule.
21. A container according to claim 19, wherein the container comprises a coating.

22. The container having a coating according to claim 21, wherein the coating is selected from cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylic acid polymers, hypromellose phthalate, hydroxypropylmethyl cellulose phthalate hydroxyalkyl methyl cellulose phthalates or mixtures thereof.

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23. Caplets encapsulated in a polymer composition according to claim 1.
24. Capsules according to claim 20, wherein that the capsule halves are sealed with one or more layers of the polymeric composition according to claim 1.
- 10 25. Capsules according to claim 20, wherein that the capsule halves are sealed by a liquid fusion process.

# INTERNATIONAL SEARCH REPORT

National Application No

PCT/US 97/22177

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C08L1/26 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 246 693 A (SHIN-ETSU CHEMICAL CO. LTD.) 25 November 1987  see page 5, line 24 - page 6, line 15 see page 7, line 25 - page 8, line 6 see abstract ---	1, 3-5, 13-16, 18-20, 23
A	BE 686 537 A (THE DOW CHEMICAL) 7 March 1967  see page 7, line 20 - line 29 see claims ---	1, 3-5, 13-16, 18-20, 23
A	GB 643 853 A (ELI LILLY AND COMPANY) 27 September 1950  see page 4, line 42 - line 48 ---	1, 3, 4, 8, 9, 14, 19, 20, 23
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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